Lung Cancer in Nonsmokers

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Among 2668 patients with newly diagnosed lung cancer interviewed between 1971 and 1980, 134 cases occurred in "validated" nonsmokers. The proportion of nonsmokers among all cases was 1.9% (37 of 1919) for men and 13.0% (97 of 749) for women, giving a sex ratio of 1:2.6. Kreyberg Type II (mainly adenocarcinoma) was more common among nonsmoking cases, especially women, than among all lung cancer cases. Comparison of cases with equal numbers of age-, sex-, race-, and hospital-matched nonsmoking controls showed no differences by religion, proportion of foreign-born, marital status, residence (urban/rural), alcohol consumption or Quetelet's index. Male cases tended to have higher proportions of professionals and to be more educated than controls. No differences in occupation or occupational exposure were seen in men. Among women, cases were more likely than controls to have worked in a textile-related job (relative risk = 3.10, 95% confidence interval 1.11–8.64), but the significance of this finding is not clear. Preliminary data on exposure to passive inhalation of tobacco smoke, available for a subset of cases and controls, showed no differences except for more frequent exposure among male cases than controls to sidestream tobacco smoke at work. The need for more complete information on exposure to secondhand tobacco smoke is discussed.

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ALTHOUGH LUNG CANCER risk is strongly associated with cigarette smoking, lung cancer does infrequently occur in nonsmokers.[1,2] Several features distinguish lung cancer in nonsmokers from that occurring in smokers. First, most cases of lung cancer in nonsmokers are found in women.[2,3] Second, the distribution of histologic types of lung cancer differs between smokers and nonsmokers. In smokers the epidermoid type predominates, whereas in nonsmokers adenocarcinoma is more common, especially in women.[2-5]

This article presents data from a case–control study of nonsmoking patients with histologically confirmed diagnoses of primary lung cancer with respect to histology, demographic factors, residence, Quetelet's index, alcohol consumption, previous diseases, occupation and occupational exposures, and, to a limited extent, exposure to the tobacco smoke of others. Due to the small number of cases and controls on whom we have information on passive inhalation, the data presented here on that question are in the nature of preliminary results. A discussion of previous studies concerning this issue emphasizes the need for obtaining more detailed information on sidestream smoke exposure and related variables.

Methods

All cases of primary cancer of the lung occurring in cases who reported never having smoked on a regular basis* were extracted from an ongoing case–control study of tobacco-related cancers conducted in a number of cities between 1971 and 1980† and described previously.[6] For each case, the hospital chart was re-examined in order to confirm the diagnosis and the absence of smoking

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* Our definition of a nonsmoker was someone who had never smoked as much as one cigarette, pipe, or cigar per day for a year.

† The majority of the cases (and matched controls) were interviewed at Memorial Hospital in New York City, 30 of the 37 male cases and 70 of the 97 female cases.

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throughout the patient's lifetime. The histologic type of lung cancer was obtained from the pathology report or the discharge summary for each case. Those cases in whom the diagnosis was not primary lung cancer or in whom there was an indication of smoking, even in the remote past, were excluded from the study. Those remaining in the study are referred to as "validated" nonsmokers.

A control was matched to each case on the basis of age (±5 years), sex, race (with 5 exceptions‡), hospital, date of interview (±2 years), and nonsmoking status. Controls were selected from a large pool of hospitalized patients who were interviewed over the same period as the cases and who had diseases which were not tobacco-related. The distribution of diagnoses among the controls was as follows: men, 62.1% other cancers, 24.3% benign neoplastic disease, 13.5% non-neoplastic disease; women, 59.9% other cancers, 14.4% benign neoplastic disease, 25.8% non-neoplastic disease.

All subjects were interviewed in the hospital with a standardized questionnaire including questions on demographic factors, occupation, occupational exposures, tobacco smoking, alcohol use, Quetelet's index (kg/cm^2 × 10,000), and history of tobacco-related diseases. Two different versions of the questionnaire were used over the 10-year period, the first from 1971 to 1976, and the second from 1976 to 1980. Differences between the two questionnaires included a longer list of occupational exposures in the later version, and a longer list of previous diseases in the earlier questionnaire (diabetes, gout, bronchitis, emphysema, hypertension, asthma, pleurisy, pneumonia, bronchiectasis, and tuberculosis) than in the later version, which included only four questions on previous diseases (chronic bronchitis or emphysema, asthma, diabetes, and elevated blood pressure).

Alcohol consumption was assessed in current drinkers and exdrinkers (combined) relative to never-drinkers and occasional drinkers (combined). Occasional drinkers were those who consumed less than 1 ounce of whiskey equivalents of alcohol per day of beer, wine, and hard liquor combined. Alcohol intake was categorized into three levels: (1) never/occasional drinking, (2) 1 to 3.9 oz/day, and (3) 4+ oz/day.

In addition, a number of questions on exposure to passive smoking were introduced in an addendum to the main questionnaire in 1978, and the addendum was revised in 1979. Thus, information on passive smoking was obtained on only a subset of the subjects, for men, 25 of 37 cases and their matched controls; for women, 53 of 97 cases and their matched controls. This number of responses was obtained for those questions included in both versions of the addendum, whereas the number of responses was smaller for the question "Does your spouse smoke?", since this question appeared in only one version and since it was not answered by those subjects who were not married, widowed, separated, or divorced (see Table 3).

‡ One oriental male case was matched to a white control; two hispanic and two oriental female cases were matched to white controls.

TABLE 1. Histologic Type of Lung Cancer in Never Smokers and Smokers

	Men (No.)	Men (%)	Women (No.)	Women (%)
Never smokers				
Kreyberg type I	13	(35.1)	20	(20.6)
Epidermoid/squamous	13	(35.1)	16	(16.5)
Large cell/giant cell	0		4	(4.1)
Kreyberg type II	20	(54.1)	72	(74.2)
Adenocarcinoma	16	(43.2)	60	(61.9)
Alveolar	4	(10.8)	12	(12.4)
Mixed (Kreyberg I & II) and undifferentiated/anaplastic	4	(10.8)	5	(5.2)
Total	37		97	
Smokers*				
Kreyberg type I	1187	(63.1)	341	(52.3)
Kreyberg type II	600	(31.9)	279	(42.8)
Mixed (Kreyberg I & II) and undifferentiated/anaplastic	95	(5.0)	32	(4.9)
Total	1882		652	

* A more detailed breakdown by histologic type is not presented for smokers because this information was not coded. For the nonsmokers this information was retrieved manually.

Differences between cases and controls were assessed by the chi-square test for independence,[7] and by the Mantel-Haenszel extension test for linear trend.[8] Point estimates of the relative risk with test-based 95% confidence intervals were calculated following Miettinen's method.[9]

Results

For the 10-year period, 1971 to 1980, among 1919 cases of primary lung cancer in men, 37 (1.9%) occurred in validated nonsmokers. Among 749 lung cancer cases in women, 97 (13.0%) were validated nonsmokers. This difference in the proportion of nonsmokers in men and women is highly statistically significant, $\chi^2(1) = 137.21$, $P < 0.001$.

Histologic Type

Table 1 shows the histologic type of lung cancer for nonsmokers and smokers by sex. Among male smokers with lung cancer there were nearly twice as many Kreyberg type I§ cases as Kreyberg type II (1187 *versus* 600), while

§ Kreyberg type I includes squamous cell, oat cell, small cell and large cell carcinomas; Kreyberg type II includes adenocarcinoma, bronchiolar, and alveolar carcinoma.

TABLE 2. Distribution of Background Variables in Cases and Controls

	Men				Women			
	Cases		Controls		Cases		Controls	
	(No.)	(%)	(No.)	(%)	(No.)	(%)	(No.)	(%)
Age								
≤49	13	(35)	12	(32)	12	(12)	15	(15)
50–59	11	(30)	12	(32)	26	(27)	24	(25)
60–69	7	(22)	10	(27)	29	(30)	34	(35)
70+	6	(14)	3	(8)	30	(31)	24	(25)
Total	37		37		97		97	
Religion								
Protestant	2	(6)	5	(14)	27	(28)	34	(36)
Catholic	16	(46)	14	(40)	31	(32)	36	(38)
Jewish	15	(43)	13	(37)	38	(40)	24	(25)
Other	2	(6)	3	(9)	0	(0)	1	(1)
Total	35		35		96		96	
Yr of education								
1–11	3	(5.4)	6	(16.2)	38	(39.2)	29	(29.9)
12	7	(16.2)	11	(29.7)	25	(27.8)	37	(38.1)
13–15	6	(21.6)	8	(21.6)	14	(15.5)	15	(15.5)
16+	20	(56.8)	12	(32.4)	16	(17.5)	15	(15.5)
Total	37		37		97		97	
Occupational status								
Professional	22	(59.5)	14	(37.8)	8	(8.2)	11	(11.3)
Skilled	6	(16.2)	7	(18.9)	26	(26.8)	35	(36.1)
Semiskilled	2	(5.4)	9	(24.3)	6	(6.2)	6	(6.2)
Unskilled	3	(8.1)	2	(5.4)	8	(8.3)	5	(5.2)
Housewife	0	—	0	—	38	(39.2)	28	(28.9)
Retired/unemployed	4	(5.5)	5	(13.5)	11	(11.3)	12	(12.4)
Total	37		37		97		97	

among female smokers the numbers were more similar (341 *versus* 279). This difference is statistically significant, $\chi^2(1) = 25.91$, $P < 0.001$. Among male never-smokers, there were 13 Kreyberg type I *versus* 20 Kreyberg type II cases, while among females, there were 20 Kreyberg type I *versus* 72 Kreyberg type II cases. Although the number of male nonsmoking cases is small, the difference between men and women is statistically significant, $\chi^2(1) = 3.90$, $P < 0.05$. Furthermore, the difference between the proportions of Kreyberg I and Kreyberg II in never-smokers compared with smokers is statistically significant in both sexes (for men, $\chi^2(1) = 10.54$, $P < 0.005$; for women, $\chi^2(1) = 35.46$, $P < 0.001$).

Age

Table 2 gives the age distribution of cases. Male cases are significantly younger than female cases ($\chi^2(3) = 11.30$, $P < 0.025$). The mean age for men was 53.9 years (SD [standard deviation] 14.3) compared with 61.6 (SD 11.3) for women. This younger age of male cases appears to hold for both Kreyberg I and Kreyberg II types: the mean age for Kreyberg I and Kreyberg II lung cancer in men was 52.8 and 53.6 years, respectively, while in women Kreyberg I had a mean age of 63.7, and Kreyberg II had a mean of 61.0 years.

Education

Kreyberg II cases appeared to be more educated than Kreyberg I cases in both sexes (data not presented).

Case-Control Comparisons

There were no differences in male cases and controls by religion, proportion of foreign born, marital status, and residence in childhood, adolescence, and adulthood. Male cases were better educated (57% of cases had gone beyond college compared to 32% of controls), and a higher proportion were professionals (60% of cases compared to 38% of controls) (Table 2). These differences did not reach statistical significance.

Female cases and controls did not differ significantly on proportion of foreign born, marital status, education, occupational status, or residence in childhood, adolescence, or adulthood. There was a nonsignificantly higher proportion of Jewish women among cases compared to their controls (40% *versus* 25%) (Table 2). In both cases and controls, the proportion of urban dwellers increased from 70% in childhood to 80% in adulthood.

History of previous diseases: No case–control differences were found for history of chronic bronchitis, emphysema, diabetes, asthma, pneumonia, or hypertension in males. In females, there were similar findings, except more female cases had a previous history of pneumonia than controls: 16/40 cases *versus* 3/38 controls ($\chi^2(1) = 10.9$, $P = 0.001$).

Quetelet's index: Quetelet's index was calculated using the subject's weight 5 years prior to diagnosis for 22 male cases and their matched controls and for 50 female cases and controls on whom this information was available. No difference was seen between cases and controls of either sex.

Alcohol: No significant differences in alcohol intake were found between cases and controls of either sex.

Occupational exposure: No differences in occupational exposures were observed between male cases and controls. In females, the only significant difference was that 14 cases reported working in a textile-related job compared to 5 controls (relative risk, 3.10; 95% confidence interval 1.11–8.64). Of the 14 female cases, 2 were diagnosed with Kreyberg I, 11 with Kreyberg II and 1 had mixed-type lung cancer. For those cases and controls interviewed between 1976 and 1980, information on the duration of exposure to occupational and environmental substances was available. There was no difference in the mean num-

ber of years of exposure in textile-related jobs (16 years) of cases and controls. Among the cases, the specific occupations were the following: one seamstress, two dressmakers, one sewing-machine operator, one assembler and yarnwinder, one dress-shop worker, two salesladies who had done factory work, one apparel manufacturer, one clothing packer, one typist, one washerette/housekeeper, one bookkeeper, and one housewife.

Among the 37 male cases only a few (5) reported exposures to substances of potentially etiologic interest. An electronics engineer had 35 years of exposure to cleaning chemicals; a designer had 25 years of exposure to chemicals and acids and 15 years of exposure to plastics and glues; a director of sales for a chemical corporation (a chemist) had 12 years of exposure to chemicals and acids; an upholsterer had 30 years of exposure to asbestos, rubber, and solvents; and a machine shop attendant had 37 years of exposure to metals, grease, and oil.

Among the 97 female cases, in addition to exposure to textile work reported by 14, few reported other exposures. The assembler/yarnwinder who reported exposure to textiles also reported exposure to metals for 28 years; a machine operator had 10 years of exposure to metals; an assistant medical technician had 10 years of exposure to chemicals and acids; a social worker had 5 years of exposure to metals and welding; an electronic prototype technician had 14 years of exposure to chemicals and acids, metals and solvents; and a chambermaid had 23 years of exposure to ammonia.

We looked separately at the small number of cases who developed lung cancer younger than age 40, eight men and six women. The occupations of the men included an accounting professor, an accounting clerk (who had been a teacher for 11 years), a neurosurgeon, a stock trader, a postal service clerk, a law student, a salesman, and a self-employed president of a supply company. None of the men reported any exposures. The female cases included two housewives, an assistant manager for the American Automobile Association, an electronic prototype engineer (mentioned above), a telephone operator, and a high school teacher. Only the electronic prototype engineer reported any exposures. The distribution of histologic types among these younger cases did not appear to differ from that of all nonsmoking cases.

Passive inhalation: Of the 25 male cases and controls who were asked about exposure to other people's cigarette smoke at home, six male cases reported having been exposed compared to 5 controls (Table 3). Eighteen of 25 cases reported having been exposed to cigarette smoke at work compared to 11 of 25 controls. The difference is just statistically significant ($P = 0.05$). Mantel extension test for linear trend in the frequency of exposure (four levels) in cases and controls gives a chi-square of 2.88, $P < 0.005$. The number of male cases and controls who

TABLE 3. Exposure to Passive Inhalation Among a Subset of Cases and Controls

	Men				Women			
	Cases		Controls		Cases		Controls	
	(No.)	(%)	(No.)	(%)	(No.)	(%)	(No.)	(%)
At home*								
Yes	6		5		16		17	
No	19		20		37		36	
Total	25		25		53		53	
At work†								
Yes	18		11		26		31	
No	7		14		27		22	
Total	25		25		53		53	
			($P < 0.045$)					
Spouse smoke‡								
Ever	5		5		13		15	
Never	7		7		11		10	
Total	12		12		24		25	

* Current exposure on a regular basis to family members who smoke.
† Current exposure on a regular basis to tobacco smoke at work.
‡ Spouse's current or past smoking habits.

reported that their wives smoked was identical, 5 of 12 in both groups. In both groups the wives had smoked for comparable periods of time.

No differences on exposure to passive smoking at home or at work were found in women, 16 of 53 cases were exposed at home compared to 17 of 53 controls, and 26 of 53 cases were exposed at work compared to 31 of 53 controls. Of the women who were asked about their spouses' smoking habits, no differences between cases and controls were found in the proportion who smoked, 13/24 for cases *versus* 15/25 for controls. Again, years of smoking in the cases' husbands did not differ from years of smoking in the controls' husbands.

Discussion

Due to the powerful role of smoking in the etiology of lung cancer, other risk factors can best be studied in nonsmokers with confirmed nonsmoking histories. Thus, a key feature of this investigation is that in order to "validate" the diagnosis of primary lung cancer (obtained from the discharge summary or the pathology report) and the nonsmoking status of all study subjects (obtained in the original interview), we went back to the hospital records and abstracted information on diagnosis and smoking history. If the chart indicated that the patient had smoked tobacco at any period of his or her life, the person was excluded from the study. In the rare instance that no mention of smoking history was found in the chart, the patient was included. Of the 156 cases of lung cancer in

our computer file of self-reported never-smokers, review of the hospital chart revealed that 13 were actually smokers or had smoked at some time, and 9 were not primary lung cancers. These 22 cases were excluded from the analysis. Confirmation of the diagnosis and nonsmoker status of the controls was carried out in the same way as for the cases. For none of the controls was the self-reported nonsmoking status contradicted by information in the chart.

The finding that more cases gave a conflicting response on whether or not they had ever smoked than controls (13 of 147 primary lung cancer cases compared to none of 134 controls) is of significance. This suggests that some lung cancer cases tend to deny a smoking history more than controls with non-tobacco-related diseases. In a study of the role of cigarette smoking in lung cancer, such denial of cigarette consumption or under-reporting, which may also take place, would tend to reduce the estimate of the relative risk. In a study of lung cancer in nonsmokers, the inclusion of cases with a smoking history (misclassification) would also reduce associations of the disease with other risk factors.

Although we attempted to eliminate all smokers from among the cases and controls by using a conservative definition of nonsmoker and by excluding any subject with a history of smoking either in the questionnaire or in the hospital chart, it is possible that some subjects who reported never having smoked actually did smoke at some time.

The current study confirms earlier findings that among lifelong nonsmokers lung cancer is exceedingly rare, and that the more conservative the definition of nonsmoker and the more detailed the smoking history, the lower is the proportion of nonsmokers found among lung cancer cases.[3]

Histologic Type

As found in earlier studies, Kreyberg type II (primarily adenocarcinoma) is more common in nonsmokers with lung cancer than in smokers and, in both groups, Kreyberg type II is more common in women. The percentages of nonsmoking cases with adenocarcinoma in our study (43% of males, 62% of females) are in close agreement with those from the American Cancer Society's prospective study (46% of males, 59% of females, L. Garfinkel, personal communication, 1982). In view of the differences in design and method of selection of subjects, this agreement suggests that these percentages may be representative of nonsmoking lung cancer cases generally.

Sex Ratio

In our nonsmoking cases there are 2.6 times as many females as males, even though the male–female incidence ratio for lung cancer is 2.4,[10] and the male–female ratio among all lung cancer cases in our file is 2.6 (1919/749). The larger number of nonsmoking women with lung cancer compared with nonsmoking men is presumably due to the historically higher proportion of nonsmokers among women compared to men. Doll found no difference in the age-specific death rate from lung cancer among nonsmoking males and females.[1] Similarly, Garfinkel[11] found no difference in the age-adjusted lung cancer mortality rate for nonsmoking men and women.

Case-Control Comparisons

Previous diseases: Our finding that female cases had a higher frequency of previous history of pneumonia compared to controls is difficult to interpret since we do not have information on the age at diagnosis or on the duration of pneumonia.

Occupation: Earlier case studies of lung cancer in nonsmokers have included occupations in males with exposure to dust and/or fumes, *i.e.*, a carpenter, a joiner, a fitter, and a flour miller among the 7 male cases in Doll's study;[1] two painters, a smelter, a blacksmith, a gasoline truck driver, a gasoline and oil delivery man and gas station attendant, a cabinet maker, a sawmill worker, and an engineer among 20 male cases in Wynder's study;[2] a plumber/steamfitter and an auto body and fender repairman among 8 male cases in the study by Wynder and Berg.[3] Among female cases, the occupations were less suggestive of exposure to inhaled substances. These studies interviewed small numbers of nonsmoking cases, and did not make use of a comparison group.

Our findings of a statistically significant threefold excess risk of lung cancer among women who reported having worked in the textile industry is of interest. Doll, in his study of lung cancer among nonsmokers, lists occupations of more than 3 years duration in 7 male and 40 female lung cancer cases. Out of 31 women who had been employed outside the home, 5 had worked as seamstresses or dressmakers.[1]

However, there is no clear relationship in our data between duration of exposure and risk of disease. The mean number of years of exposure was the same for cases and controls. Most importantly, it is not clear that there is a single exposure or group of exposures that all of the workers in textile-related jobs have in common.

Furthermore, it should be emphasized that our occupational data are limited since there was room only to code one occupation—that of longest duration—and two exposures. Occupational and environmental exposures to specific substances were obtained by asking the subjects whether they had ever been exposed for more than a year to any of a list of substances. Self-reported exposures of this kind are subject to information bias since awareness of such exposure could be expected to vary with the in-

dividual, with educational level, with different jobs, and between cases and controls. In only 7 of the 14 cases did the coded occupation mention textile work. The remaining seven cases reported occupations not specifically associated with textiles, such as "typist," but reported exposure to textiles. Evidence from existing occupational studies of lung cancer risk in textile workers is scant.[12-14] No cohort study of textile workers appears to have been carried out.

The apparently minor role of occupational exposures in our male cases is consistent with the high percentage of professionals (60%) among them. Although our data do not suggest an important role of occupation or exposure to specific substances, it would be desirable in the future to obtain more detailed and objective occupational histories on cases of lung cancer occurring in nonsmokers.

Passive inhalation: The plausibility of a role of passive inhalation in lung cancer can be questioned on several grounds. Although sidestream cigarette smoke contains higher concentrations of toxic components than mainstream smoke,[15] it is diluted in the ambient air to varying degrees (depending on the size and shape of the room, proximity to the smoker, and ventilation) by the time it reaches the passively exposed person. As shown by Auerbach and coworkers,[16] the changes in the bronchial epithelium characteristic of smokers are rarely observed in lifetime nonsmokers.

Nevertheless, the possibility that heavy exposure to secondhand smoke over a long period of time could lead to increased cancer risk cannot be ruled out at present. Because questions on passive inhalation were introduced in our questionnaire in 1978, we only have information on this factor for between 28% and 68% of our subjects depending on the specific question. We present the distributions of responses to these questions as preliminary data since the numbers are small. Cases do not differ from controls except for the greater exposure to cigarette smoke at work reported by male cases compared to male controls. Those cases who reported passive inhalation exposure did not differ in their distribution of histologic types from unexposed cases. The difference between exposure to cigarette smoke at work between male cases and controls could be due to information bias, although there is no indication of such bias in the responses to the other questions on passive inhalation.

The studies which, to date, have addressed the issue of passive inhalation and lung cancer have differed in methodology, the population studied, the type of lung cancer studied, the degree of histologic confirmation, and in results. These studies are summarized in Table 4. They have been commented on by a number of investigators.[11,17-19] We wish to draw attention here to several points which are crucial in assessing a contribution of passive smoking to lung cancer and which need to be considered in future studies. First, the proportion of histologically confirmed diagnoses in the studies listed in Table 4 ranged from 35% (Trichopoulos *et al.* [20]) to 82% (Chan and Fung [21]). Given the difficulty of diagnosing lung cancer, histologic confirmation is essential. Second, Trichopoulos *et al.*[20] excluded adenocarcinoma and terminal bronchiolar cases, whereas adenocarcinoma predominated in Hirayama's cases[22] (personal communication, 1981), in those of Chan and Fung,[21] and in our cases. In the American Cancer Society study reported by Garfinkel,[11] histologic type was obtained for lung cancer cases during the first 6 of 12 years of the study. Seventy percent of these cases had histologic confirmation but some of these were only identified as "carcinoma." Among the cases with confirmed histology and information on specific cell type, 46% of the male and 59% of female nonsmokers had adenocarcinoma compared to 23% among male and 46% among female smokers (personal communication). Since little is known about the etiologic significance of different histologic types and since the distribution of types differs in different populations, it is premature to restrict studies of passive inhalation to particular types.

Third, although histologic classification of lung cancer is imperfect, it is desirable to stratify by the major histologic types in the analysis if the number of cases permits since different histologic types may have different etiologies.

Finally, all of the previous studies used the amount and duration of spouse's smoking as the measure of exposure to passive inhalation. Focus on the spouse's smoking may fail to provide an adequate measure of the subject's exposure for a number of reasons: (1) a subject's actual exposure depends on how much time the smoking spouse smokes in his or her immediate presence; the spouse could be a heavy smoker but spend very little time at home; (2) in addition to the current spouse's smoking habits, those of former spouses may be equally important; (3) the subject may live with other relatives who smoke; (4) exposure to tobacco smoke at work can be a substantial proportion of a person's exposure; (5) exposure in cars, commuter trains, buses, and in other situations, such as restaurants, movie theaters, etc., could be significant. It is for these reasons that we have recently revised our questionnaire to include detailed questions which will give a more complete picture of the subject's exposure, both in respect to different environmental settings and to duration of exposure for each specific component.

If passive inhalation in nonsmokers is associated with increased lung cancer risk, by what mechanism does it exert its effect? Since adenocarcinoma is the most common histologic type of lung cancer in nonsmokers, one could hypothesize that inhaled sidestream smoke increases

TABLE 4. Summary of Studies of the Role of Passive Inhalation in Lung Cancer in NonSmokers

Author/ type of study/ population	No. of cases	Histology	Findings	Comments
Hirayama (1981)[22] Prospective/ Japanese nonsmoking wives aged 40+ years	174 deaths in married nonsmoking women w/lung ca among 91,540 nonsmoking married women	Out of a sample of 23 cases, 17 were adenocarcinoma	A dose-response relationship was seen between the nonsmoking wives' risk and the husbands' smoking habit: wives of exsmokers or of 1–19 cigs/day-smokers had RR = 1.61; wives of smokers of ≥20 cigs/day had RR = 2.08	Exposure index was based on smoking habits of husbands
Garfinkel (1981)[11] Analysis of data from two prospective studies/ACS population and Dorn study of veterans[11]	195 deaths from lung ca among male nonsmokers; 564 deaths from lung ca among female nonsmokers (ACS); 168 lung ca deaths among nonsmokers (Dorn)	Histologic confirmation of dx in 69% of cases in first 6 years of ACS study. Among lung cancer cases with confirmed detailed histology, 46% of male and 59% of female nonsmokers had adenocarcinoma compared with 23% of male and 46% of female smokers (personal communication)	No significant increase in lung ca risk seen in nonsmoking wives of smoking husbands compared with nonsmoking wives of nonsmoking husbands	Exposure index was based on smoking habits of husbands
Trichopoulos *et al.* (1981)[20] Case-control/white female residents of Athens, Greece	40 female nonsmokers w/lung ca other than adenoca or terminal bronchiolar	14 cases were histologically confirmed; 19 were cytologically confirmed; 18 were clinically confirmed; excluded adenocarcinoma and terminal bronchiolar	RR of lung ca associated w/ having a husband who smokes <1 pack/day was 2.4; RR associated w/ having a husband who smokes >1 pack/day was 3.4. (χ^2 for linear trend = 6.45; $P < 0.02$)	Exposure index was based on smoking habits of husbands and former husbands
Chan and Fung[21] Case-control/ Hong Kong Chinese	Only two nonsmokers out of 208 male lung ca cases; 84 nonsmokers out of 189 female lung ca patients	15 of the 84 female cases were squamous or epidermoid ca; 38 were adenocarcinoma; 15 had no histologic verification	Among nonsmoking women the proportion of cases whose spouse smoked was slightly lower than that of controls (34 of 84 or 40.5% *vs* 66 of 139 or 47.5%). Among nonsmoking women, there was no significant difference in the proportion of cases who used kerosene fuel in cooking compared with controls.	It is unclear what question was used regarding inhalation since in an earlier paper*, the question is given as "Are you exposed to the tobacco smoke of others at home or at work?"; whereas here reference is made only to "smoking habits of spouses." No information is given on how many subjects were married

Ca: cancer; dx: diagnosis; cigs: cigarettes; RR: relative risk; *vs*: *versus*.
* Chan WC, Colbourne MJ, Fung SC, Ho HC. Bronchial cancer in Hong Kong 1976–1977. *Br J Cancer* 1979; 39:182–192.

the risk for this type. Volatile components of cigarette smoke, including volatile nitrosamines, are more likely than respirable particulate matter to reach the periphery of the lung. Current findings suggest most lesions in nonsmokers are located in the deeper portions of the lung. Nonsmokers exposed to cigarette smoke in enclosed spaces are reported to have increased levels of carbon monoxide in their blood,[23–25] which suggests that other volatile components could reach the lung. It would be important to know in this regard whether the location of lesions in the lungs of nonsmoking lung cancer cases with exposure to passive inhalation differs from that among smokers.

In addition to the etiologic factors discussed in this article, other possible explanations of the occurrence of lung cancer in nonsmokers should also be considered.

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Exposure to ionizing radiation in the course of radiation treatment could be responsible for some cases. Also, Auerbach and coworkers[26] have suggested that lung cancer could arise in nonsmokers secondary to healed tuberculosis scars, although this is unlikely to account for many cases.[27] Another possibility is that lung cancer in nonsmokers, especially adenocarcinoma, is estrogen-related since it is more common in women than in men. It has been shown that adenocarcinoma of the lung frequently contains estrogen receptors.[28] Still another possibility is that carcinogens of nutritional origin could be carried to the lung by the blood. These possibilities deserve epidemiologic exploration.

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Vilter Symposium: Lymphomas

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This symposium will be held at the Westin Hotel, Cincinnati, Ohio. Direct inquiries to: Orlando J. Martelo, MD, FACP, Director, Hematology-Oncology Division, 6367 University of Cincinnati College of Medicine, 231 Bethesda Avenue, ML #562, Cincinnati, OH 45267 (513) 872–4233.

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